Presentation and Management of Uncomplicated vs Complicated Gram Positive Bacteremias

CSHP Symposium June 2020

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Presenter Disclosure

• I have **no** current or past relationships with commercial entities
• **Have** received a speaker’s fee from CSHP-BC for tonight’s session
Commercial Disclosure

• This learning activity has received no financial or in-kind support from any commercial or other organization.
Acronyms

- GGS - Group G Streptococcus
- SAB - Staphylococcus aureus bacteremia (MSSAB, MRSAB)
- IE - infective endocarditis
- TTE: transthoracic echocardiograph
- TEE: transesophageal echocardiograph
- TTP - time to positivity
- DAP or Dapto - daptomycin
- Vanco - vancomycin
- BCx - blood cultures
- r/o - rule out
- Pip-tazo - piperacillin-tazobactam
Learning Objectives

1. Apply a systematic approach to bacteremia to 2 patient cases
2. Identify which pathogens and host factors are associated with a more tenuous clinical course
3. Distinguish uncomplicated from complicated Staph aureus bacteremia
**General Approach**

1. **Find the source**
   - Localizing symptoms or
   - Bug – gram negative vs gram positive
   - Patient risk factors – hardware, lines, recent procedures, pre-existing medical conditions

2. **Control the source**
   - OR- intraabdominal, chronic wound debridement etc
   - Removal of hardware (urinary catheter, PICC line unless compelling need to salvage etc)
   - Repeat blood cultures to confirm controlled (some bugs/clinical scenarios)

3. **Effective drug therapy**
   - Cover bacteremia and the source
   - Preferred drugs/PK profile

4. **Further investigations**
   - ECHO, intraabdominal imaging
   - Secondary seeding
Easy Bacteremias

Examples:

- **Uncomplicated pyelonephritis:**
  - 73 year old female presents with 2-3 days of fevers, flank pain, vomiting
  - Urine culture + E coli, blood cultures + 2/2 E coli
  - Defervesces and inflammatory markers drop significantly within 48h on IV ceftriaxone
  - Switch to amox-clav day 3, complete a total of 7 day course of antibiotics

- **Catheter-associated UTI:**
  - 83 yo male with chronic foley presents with 24h of fever, suprapubic pressure, flank pain
  - WBCs up to 19 in ED, CRP up to 250. Urine culture + Klebsiella pneumonia, blood cultures + same 2/2
  - Catheter changed. Responds well to IV ceftriaxone. Prostatitis ruled out on exam
  - Switch to amox-clav day 3, complete total of 10 day course
Easy Bacteremias

Examples:

- **Cholangitis with early Endoscopic retrograde cholangiopancreatography (ERCP):**
  - 79 year old male presents with 2d history of fevers, rigors, jaundice, RUQ pain
  - Imaging shows choledocholelithiasis, CBD (common bile duct) dilated to 10mm. Blood + 2/2 Kleb variicola
  - Given ceftriaxone, defervesces. ERCP done on day 4 of admission
  - Stepdown to amox-clav within 24h of ERCP, complete 7 days total

- **Uncomplicated pneumonia:**
  - 38 year old female presents with 4d history of purulent cough, SOB, pleuritic chest pain
  - In ED, O2 up to 4L/min, WBCs ↑22, HR up to 130s. CXR+ consolidation LLL. Blood cultures + Strep pneumo 2/2.
  - Defervesces after 48h of ceftriaxone, CRP and inflammatory markers drop rapidly on antibiotics
  - Switch to oral amoxicillin to complete 7 day course total
Harder Bacteremias

High Risk Pathogens

- Duke Major Criteria pathogens for endocarditis: Enterococcus, Staphylococcus, Viridans group Strep
  - Also more prone to seeding other spaces, e.g. joints, bones (vertebrae in particular)
- Candida, Strep anginosus for other types of secondary seeding

“High Risk” Hosts/Situations

- Patient unable to localize symptoms
- Not experiencing localizing symptoms
- Hardware especially cardiac and spinal
- Community-onset (unclear duration of bacteremia)
Index of Suspicion for Deep Infection

- **Bacteremia that sustains on effective antimicrobial therapy**
  - Staphylococcal bacteremia *unclear source* with hardware
  - Enterococcal bacteremia *unclear source* with hardware
  - Staphylococcal or Enterococcal bacteremia clear source, hardware
  - Viridans Strep bacteremia unclear source
  - Staphylococcal or Enterococcal bacteremia clear source, no hardware
  - Beta-hemolytic Strep bacteremia unclear source, hardware
  - Beta-hemolytic Strep bacteremia unclear source, no hardware
  - Beta-hemolytic Strep bacteremia clear source
  - Gram negative bacteremias unclear source, hardware
  - Strep mitis or salivarius bacteremia of clear dental source, no hardware
  - Gram negative bacteremias unclear source, no hardware
- **Gram negative bacteremias with clear source, Strep pneumo bacteremia with clear pneumonia**
Patient 1: Mr. G

- 85yo male brought to ED from work after falling due to left leg weakness
- Reported 1 day history of tactile fevers, chills, fatigue

PMHx: previous remote DVT in L lower leg, prev cellulitis L lower leg, HTN, Dual lead pacemaker placed Nov 2008 for sick sinus. No IVDU.
- Doppler is done in ER, negative for DVT

O/E
- Significant erythema to L leg, including to the top of the foot and extending up the shin. Associated edema.
- Blood cultures are drawn and he’s started on ceftriaxone
- These subsequently return positive 2/2 Group G Strep, TTP=12h

Labs on arrival 4 Sept:
- Lactate: 3.0 mmol/L
- CRP: 132

Current Vitals:
- HR= 133, BP=125/63
- Tmax 24h=39.5

C&S: Blood Group G Strep 2/2, TTP=12h

Imaging: Lower extrem US/doppler (-) DVT, but marked edema, prominent lymph nodes in left inguinal region
Patient 1: Mr. G
Which of the following would you NOT do for your patient with GGS bacteremia?

A. Repeat blood cultures x 2 sets
B. Evaluate pacemaker pocket with nurse
C. Suggest TTE
D. Ask patient about other localizing symptoms (pain to joints, back)
Next Steps

• Lower risk pathogen with respect to metastatic seeding; host has hardware

• **Find the source:**
  • Clear signs of cellulitis and a classic cellulitis pathogen. Source appears obvious
  • **Evaluate pacemaker pocket** for anyone with a pacemaker, but this distal to the procedure, not likely
  • Evaluate for any other *localizing symptoms* to rule out other possible foci

• **Control the source:**
  • Not a pathogen particularly prone to abscesses and no signs of source control issues as of yet
  • Given pacemaker, ensure clearance to ensure no source control issue – *repeat blood cultures*

• **Effective Drug Therapy:**
  • On ceftriaxone empirically which covers GGS universally, while further workup and evaluation is being done

• **Further Investigations**
  • No signs of source control issue yet
  • No additional signs of secondary seeding (eg no lower back pain)
  • Have to keep the pacemaker in the back of our mind and make an assessment re the risk of this, but given clear source and not a pathogen particularly prone to pacemaker infection, **don’t need to ECHO upfront**
Mr. G – 72h into admission

- Defervesced rapidly, no fevers after initial day in ER
- Repeat blood cultures clear
- Subjectively, patient feels improved, but L leg redness visibly mildly expanded over previous 24-48h
- Fluid filled blisters forming, some new red streaking
- Edema modestly improved, no expansion beyond margin of erythema
- MRP approaches you asking if you should broaden antimicrobials

Vitals:
- HR 90s, BP 130/78
- Tmax 24h=37.2

Lactate: 2.1 mmol/L
CRP= 282

Repeat blood C&S: negative x 2 sets after patient had received 1.5 days of ceftriaxone
What is the most likely explanation for rise in inflammatory markers 72h into admission?

A. Antibiotic failure
B. Possible abscess/source control issue at site
C. Possible pacemaker infection
D. Natural progression in host inflammatory response
E. Compartment syndrome
F. Necrotizing infection
What is the most likely explanation for rise in inflammatory markers 72h into admission?

A. Antibiotic failure- universal susceptibility to beta-lactams
B. Possible abscess/source control issue at site- worth considering, but low risk pathogen and early in course for this
C. Possible pacemaker infection- worth considering, but early to rule in pacemaker infection when a plausible source is present with a lower risk pathogen
D. Natural progression in host inflammatory response- CRP takes ~48h to 72h to peak, and it is common in the first 48h of hospitalization to see the WBCs rising
E. Compartment syndrome- no numbness, no foot drop, no claw foot, not sufficiently tense
F. Necrotizing infection- too late in the clinical picture. After 72h, this would have become obvious and there would have been clinical decompensation. Pain was not out of proportion with touch, and only mild expansion at the site not rapid.
What is your antibiotic plan for GGS cellulitis with ongoing elevation in inflammatory markers?

A. Add vancomycin
B. Add clindamycin
C. Broaden to pip-tazo or meropenem
D. Change to Penicillin G
E. Change to oral amoxicillin
What is your antibiotic plan for GGS cellulitis with ongoing elevation in inflammatory markers?

A. Add vancomycin- if we had not treated MRSA that was present in the last 72h, we would expect deterioration and worsening in findings.

B. Add clindamycin- some clinicians do for a few days even outside of necrotizing soft tissue infections, for other benefits (toxin inhibition and eagle effect)

C. Broaden to pip-tazo or meropenem- neither of these drugs will provide any benefit over penicillin itself for GGS. These drugs provide more coverage against gram negatives via inhibition of beta-lactamases or stability against hydrolysis by beta-lactamases. No benefits compared to penicillin itself against Strep- Group G Strep does not produce beta-lactamases.

D. Change to Penicillin G – universally susceptible

E. Change to oral amoxicillin- a bit early for this, prior to seeing clear ongoing improvement
Mr. G- 7 Days Later

- Patient states feeling better and able to actually weight bear
- Open blisters at site with weeping, visible pronounced inflammation (unable to provide picture of patient due to privacy restrictions)

Vitals:
HR 80-90, BP 130/75
TMax 24h=37.1

Lactate: 1.9 mmol/L
CRP= 189 after 8d of Abx (peaked 337)

Labs 12Sept:

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What is the most likely reason for slow decline in inflammatory mediators?

A. Possible abscess/source control issue
B. Bullous nature of the infection
C. Pacemaker infection
What is the most likely reason for slow decline in inflammatory mediators?

A. Possible abscess/source control issue- worth keeping in mind, but no areas of fluctuance, not a pathogen particularly prone to abscesses, and clear evidence of why inflammatory markers may be elevated

B. Bullous nature of the infection- clearly an inflammatory process and unsurprising to see elevated inflammatory markers in this setting

C. Pacemaker infection- always worth considering, but so far we have a plausible explanation for the current clinical course, and again, this is a lower risk pathogen for this though certainly it happens and is very possible
Duration: Non-purulent SSTIs, unbroken skin

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<tr>
<th>Severity</th>
<th>Description</th>
<th>Duration</th>
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<tr>
<td>Mild</td>
<td>No systemic signs of infection</td>
<td>5 days</td>
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<tr>
<td>Moderate</td>
<td>Systemic findings: fever, ↑WBCs, ↑CRP</td>
<td>7 days</td>
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<tr>
<td>Bullous</td>
<td>Characteristic blistering and ongoing elevations in inflammatory markers after a few days of therapy</td>
<td>7+ days, determined by clinical course</td>
</tr>
<tr>
<td>Severe</td>
<td>Systemic findings + hemodynamic instability</td>
<td>7+ days, determined by clinical course</td>
</tr>
<tr>
<td>Necrotizing</td>
<td>Pain disproportionate to stimuli, rapid progression, purple bullae 2° to small vessel clotting and necrosis</td>
<td>Determined by nature of and success of surgical intervention, and by clinical course</td>
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**Bacteremia:** In the absence of aggravating factors (e.g. signs of secondary seeding), treat Streptococcal bacteremia secondary to an SSTI as you would treat the source infection itself.

PO Stepdown is reasonable once there is clinical improvement and we’ve ruled out deep focus/source control issue.
Oral Stepdown: Beta-hemolytic Strep Bacteremia

- Minimal literature on this
- Small studies, mostly retrospective in nature
  - Recent n=100 study in 2019 compared highly bioavailable oral agent to less bioavailable agent, showed no difference in treatment outcomes
- With the advent of OVIVA and POET, everyone has become more comfortable with oral therapy even in invasive infections
- Even prior to OVIVA and POET, most ID practitioners would be willing to stepdown to oral therapy in B-hemolytic Strep Bacteremia

Open Forum Infectious Diseases, ofz386, https://doi.org/10.1093/ofid/ofz386
Mr. G: Take Home Messages

1. Uncomplicated bacteremias have:
   - Clear plausible source (GGS + cellulitis)
   - No concerns for source control issue (clinical course matched expected course)
   - Lower risk pathogen for seeding → no or minimal further investigations (eg GGS=no need for indiscriminate ECHO)

2. Hardware, in particular cardiac hardware, always necessitates special consideration in the setting of bacteremia, must carefully consider risk of having seeded this site
   - Do not need indiscriminate ECHO, however

3. Bullous cellulitis can have a slow decline in inflammatory markers, this is not antibiotic failure or a sign of source control issue, it is the expected clinical course in this setting

4. Oral stepdown in the setting of beta-hemolytic Strep bacteremia is reasonable once deep source has been precluded, and commonly done in practice
Patient 2: Mr. F

- 69 yo M admit with several days of tactile fevers, worsening dysuria in context of known BPH and indwelling catheter
- On arrival, temp up to 40 and WBCs 18.5
- New atrial fibrillation in ER requiring amiodarone drip, troponins up to 4800 with associated EKG changes

PMHx: BPH and chronic indwelling foley. No IVDU.

O/E
- Significant abdominal pain with guarding and mild distention, RLQ > LLQ
- Initially started on pip-tazo, then BCx went + 2/2 MRSA TTP=12h, abx changed to vancomycin accordingly

Labs on arrival 4 Sept:

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<th></th>
<th>129</th>
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<th>22</th>
<th>18.5</th>
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<td>CRP</td>
<td>3.3</td>
<td>14</td>
<td>198</td>
<td>6.3</td>
<td>198</td>
<td>18.5</td>
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Lactate: 4.8 mmol/L
CRP = 336

Current Vitals:
- HR = 100-120, BP = 110-140s/60-80s
- Tmax 24h = 40.8
- C&S: Blood: MRSA 2/2, TTP = 12h. Vanco
- MIC = 1.5mg/L; urine + MRSA
- Imaging:
  - AXR = ?R renal calculus
What are your next steps for this MRSA bacteremia?

• Cannot do this via zoom, but just think through any steps that come to mind.
Next Steps

• High risk pathogen highly predisposed to metastatic foci and source control issues

Find the source:
• Localizing symptoms to GU and abdomen, but Staph aureus is NOT a GU pathogen.
• If suspected GU source with SAB, there’s usually a prostatic abscess or perinephric abscess etc (even with urinary catheters) → CT abdo/pelvis
• Acute new arrhythmia and NSTEMI: may be in setting of sepsis, but concerning for possible cardiac involvement

Control the source:
• Identify all hardware, stents, prosthetic material and remove any hardware possible (*foley cath)
• Repeat blood cultures stat and then q48h until clear to identify source control issues

Effective Drug Therapy:
• Vancomycin for this patient as confirmed MRSA

Further Investigations
• TTE (then r/a need for TEE)
• Additional infectious sources/foci? → speak to patient to r/o localizing symptoms, particularly critical with SAB
• ID/expert consult – identify further metastatic foci, reduces mortality in the literature
Mr. F: 72h after starting vanco

- Defervesced after 48h
- Foley changed
- Blood cultures have still sustained even after 48h of vanco, MRSA 2/2, TTP still 12h

CT chest/abdo/pelvis

- Large multiloculated peripherally enhancing fluid collection around prostate 7.6 x 5.1 x 3.6 cm (~75mL)
- Large pericardial effusion, 1.7cm in maximal thickness, enhancement of visceral and parietal pericardium suggestive of pericarditis
- Small bilateral pleural effusions, focal consolidation in RML, ?central cavitation and nodular infiltrate in lingula

Labs 7Sept:

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<th>CRP</th>
<th>WBC</th>
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Lactate: 2.7 mmol/L
CRP = 388

Vitals:
HR 90s, BP 130/78
TMax 24h=37.6
Repeat blood C&S: still positive done yesterday after 48h of vanco
Mr. F: 72h after starting vanco cont’d

- No new onset back pain, no pain to joints, no focal neurologic abnormalities
- Urology consulted to drain prostatic abscess
  - Drained partially and decreased in size to around 45mL post-drainage
- TEE (done after TTE):
  - Cannot exclude vegetation on mitral valve. Moderate to severe mitral regurgitation.
  - Tricuspid valve poor visualization. Aortic valve trileaflet with no valvular vegetation
  - Moderate pericardial effusion, no indications of tamponade

**Labs 7Sept:**

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Lactate: **2.7 mmol/L**
CRP= **388**

**Vitals:**
HR 90s, BP 130/78
TMax 24h=37.6

**Repeat blood C&S:** still positive done yesterday after 48h of vanco
Is this a complicated or uncomplicated SAB?

A. Complicated  
B. Uncomplicated
Is this a complicated or uncomplicated SAB?

<table>
<thead>
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<th>Uncomplicated:</th>
<th>Complicated:</th>
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<tr>
<td>Treatment duration=14 days IV from first negative BCx</td>
<td>Treatment duration 4-6 weeks IV from first negative BCx</td>
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<tr>
<td>Defervesce within 72h</td>
<td>&gt;72h to defervesce</td>
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<tr>
<td>Bloodstream cleared within 72h</td>
<td>Persistent bacteremia</td>
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<td>No metastatic foci</td>
<td>Seeding source or metastatic foci of infection</td>
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<td>No hardware or removal of hardware</td>
<td>Positive Duke criteria or ECHO for infective endocarditis</td>
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<tr>
<td>No evidence of infective endocarditis</td>
<td>Non-IE deep source of infection (osteomyelitis)</td>
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<tr>
<td>Patients without active malignancy or immunosuppression</td>
<td>Immunocompromise</td>
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<tr>
<td>No deep-seated infection</td>
<td>Failure to meet any of the criteria for uncomplicated</td>
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Deep abscess: duration also depends on radiographic resolution of abscess

*Arch Intern Med.* 2003;163(17):2066-2072
Mr. F: Update days 8-17 of admission

• After 7 days of vanco, blood cultures had still sustained + MRSA 2/2, TTP 12h in 1 set, 18h in the other
• Switched to daptomycin day 7 accordingly
• Sustained for an additional 5 days on this therapy, cefazolin added for synergy then cleared finally 5 days later, after a total of 17 days bacteremic on effective therapy

Vitals:
- HR 70s-80s, BP 130s/70s
- Tmax 24h=38.1 but mostly low 37s

Repeat blood C&S: finally cleared after 17 days bacteremic

Lactate: 1.9 mmol/L
CRP= 133

Labs 7Sept:
Sustained MRSA Bacteremia: Salvage Regimens

• Various regimens proposed in case series
• Daptomycin 1st line salvage when failing vanco (sustained after 7d)
• Dapto + beta-lactam synergy
  • Various case series and small studies had proposed benefit of daptomycin & various beta-lactams (BLs)
  • CAMERA-2 study 2020: dapto or vanco + BL x7d (intervention), vs dapto or vanco monotherapy (control)
    • Halted early due to increased AKI in the intervention arm with no reduction in mortality
    • Bacteremias were largely SSTIs or “primary”- lower probability of observing benefit for combination therapy
    • Only n=27 in intervention arm received cefazolin. Post-hoc analysis demonstrated fairly minimal AKI in cefazolin group (3.7% as opposed to 27% in the flucloxacillin and cloxacillin group)
• Ceftaroline monotherapy reasonable
• Ceftaroline + dapto more often done as few people will withdraw a therapy when failing dapto, more likely to add
  • Small n=40 pilot study: significant reduction in mortality with ceftaroline + dapto compared to vancomycin alone, (or dapto alone, but this group had n=2 and used low dose dapto)
• Ceftobiprole- not much literature

JAMA. 2020;323(6):527-537
DAP + B-lactam Pharmacologic Basis

• Beta-lactam ↑ net surface negative charge on the bacterial cell wall = ↑ binding of the positively charged dapto-Ca+2 complex + insertion into membrane

• Beta-lactam = ↑host peptide–mediated innate immune response against MRSA

• In vitro studies suggest delay in resistance to dapto/delay in rise of MIC

Ther Adv Infect Dis. 2019;6:2049936119886504
Sustained MRSA Bacteremia: Salvage Regimens

• Ceftobiprole: pending RCT with expected publication August 2021 comparing ceftobiprole to daptomycin (NCT03138733)
  • 5th Gen beta-lactam with binding affinity for PBP2a (MRSA) and PBP2x (Strep pneumo); stable against AmpC, degraded by ESBLs and MBL/KPC/OXA (various more broadly hydrolytic beta-lactamases)
  • Possible synergy with dapt and other agents
  • Preliminary data suggests more aggressive dosing than the currently approved dose may be needed for high inoculum infections
Mr. F: Update on day 28 of admission, BCx clear x 9 days

- BCx clear on 6 repeat sets (q48h)
- Subjectively well, no pain
- Repeat CT a week ago: known septic emboli, prostate abscess down to 20mL
- CRP goes up, has occasional temps into low 38s after having defervesced
- Team calls and wants to add pip-tazo

Labs 7Sept:

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Lactate: 1.6 mmol/L
CRP= 183 (had gone as low as 110)

Vitals:
HR 70s-80s, BP 130s/70s
TMax 24h=38.1 but mostly low 37s
Repeat blood C&S: finally negative after 17d bacteremic
Mr. F: Overarching clinical course

- 69 yo M with complicated MRSAB that sustained for 17d on effective therapy, currently on cefazolin and daptomycin. Blood cultures clear x 9 days now, repeated documented clearance.
- Numerous infectious foci identified: large prostatic abscess (probable original source) which was partially drained, metastatic foci to lungs with known septic emboli on a recent CT, endocarditis, and pericarditis
- Had defervesced previously, now has new low grade fevers and a rising CRP (110→183)
Which of the following will you NOT do?

A. Add pip-tazo while awaiting further investigations to cover for additional nosocomially-acquired infection
B. CT chest/abdo/pelvis to evaluate known prostate abscess and assess for new seeding
C. Talk to patient to inquire about new localizing symptoms
D. Repeat blood cultures x 2 sets
Which of the following will you NOT do?

A. **WON’T** add pip-tazo while awaiting further investigations to cover for additional nosocomially-acquired infection - he’s stable, has numerous pre-existing identified infectious foci, and team reports no new localizing symptoms

B. **WILL** CT chest/abdo/pelvis to evaluate known prostate abscess in case it’s not shrinking and we need urology consult, and to assess for further metastatic foci. We know he’s got high burden of Staphylococcus and has this abscess, so even though the bacteremia has cleared in theory, he may still be transiently bacteremic and still has risk for seeding.

C. **WILL** talk to patient to inquire about new localizing symptoms - I trust the teams, but sometimes you’ll glean really helpful info from patient, so I always triangulate stories and go talk to the patient myself, especially if I’m recommending against broadening in a febrile patient

D. **WILL** repeat blood cultures x 2 sets - worth doing to see if he’s seeding to blood again, as again this would be worrisome for a new source vs need for source control procedure again, and also impacts treatment duration
Mr. F- Final Update

• No additional pain or localizing symptoms
• Repeated his CT and found the known septic emboli along with a few new nodular areas suspicious for some new embolic events, prostate abscess much reduced in size
• No worsening SOB, no signs of fluid overload, no signs of acute heart failure
• Recently discharged from hospital after completing 6 weeks of therapy from his first negative blood cultures, 8.5 weeks of therapy total
1. Staph aureus can cause infection in virtually any body system, it is critical to get a reliable history to identify all plausible sources and metastatic foci

2. SABs are highly prone to source control issues. Almost invariably require further investigations.
   - **Must** repeat blood cultures to document clearance & get a sense of the extent of the source control problem
   - Remove hardware wherever possible
   - ECHO
   - Low threshold to image or evaluate any area with localizing symptoms

3. MSSAB has no salvage regimens. Cloxacillin or cefazolin are drugs of choice. MRSAB has several salvage regimens with data from case series, retrospective studies, and more recently the CAMERA-2 RCT

4. Duration of therapy in SAB depends on whether the patient meets criteria as uncomplicated (14 days from first negative BCx) or complicated (4-6 weeks from negative BCx)